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☐	L1	hsp near10 alpha2M	2

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L12: Entry 10 of 31 File: PGPB Apr 15, 2004

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TITLE: Alpha (2) macroglobulin receptor as a heat shock protein receptor and uses thereof

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INVENTOR-INFORMATION:

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CLAIMS:

What is claimed is:

1. A method for identifying a compound that modulates an HSP-.alpha.2M receptor-mediated process, comprising: (a) contacting a test compound with a heat shock protein and an alpha (2) macroglobulin receptor; and (b) measuring the level of alpha (2) macroglobulin receptor activity or expression, such that if the level of activity or expression measured in (b) differs from the level of alpha (2) macroglobulin receptor activity in the absence of the test compound, then a compound that modulates an HSP-.alpha.2M receptor-mediated process is identified.

2. The method of claim 1, in which the compound identified is an antagonist which interferes with the interaction of the heat shock protein with the alpha (2) macroglobulin receptor, further comprising the step of: (c) determining whether the level interferes with the interaction of the heat shock protein and the alpha (2) macroglobulin receptor.

3. The method of claim 1, in which the test compound is an antibody specific for the alpha (2) macroglobulin receptor.

4. The method of claim 1, in which the test compound is an antibody is specific for alpha (2) macroglobulin.

5. The method of claim 1, in which the test compound is an antibody is specific for a heat shock protein.

6. The method of claim 1, in which the test compound is a small molecule.

7. The method of claim 1, in which the test compound is a peptide.

8. The method of claim 7, in which the peptide comprises at least 5 consecutive

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amino acids of the alpha (2) macroglobulin receptor (SEQ ID NO.: 7).

9. The method of claim 7, in which the peptide comprises at least 5 consecutive amino acids of alpha (2) macroglobulin (SEQ ID NO.: 4).

10. The method of claim 7, in which the peptide comprises at least 5 consecutive amino acids of a heat shock protein sequence.

11. The method of claim 1, in which the compound is an agonist which enhances the interaction of the heat shock protein with the alpha (2) macroglobulin receptor.

12. The method of claim 1 in which the HSP-.alpha.2M receptor-mediated process affects an autoimmune disorder, a disease or disorder involving disruption of antigen presentation or endocytosis, a disease or disorder involving cytokine clearance or inflammation, a proliferative disorder, a viral disorder or other infectious disease, hypercholesterolemia, Alzheimer's disease, diabetes, or osteoporosis.

13. A method for identifying a compound that modulates an HSP-.alpha.2M receptor-mediated process, comprising: (a) contacting a test compound with a heat shock protein and an alpha (2) macroglobulin receptor-expressing cell; and (b) measuring the level of alpha (2) macroglobulin receptor activity or expression in the cell, such that if the level of activity or expression measured in (b) differs from the level of alpha (2) macroglobulin receptor activity in the absence of the test compound, then a compound that modulates an HSP-.alpha.2M receptor-mediated process is identified.

14. The method of claim 1 or 13 wherein the alpha (2) macroglobulin receptor activity measured is the ability to interact with a heat shock protein.

15. The method of claim 13 wherein the heat shock protein is non-covalently associated with an antigenic peptide and the alpha (2) macroglobulin receptor activity measured is the ability to re-present the antigenic peptide.

16. The method of claim 13 wherein the heat shock protein is non-covalently associated with an antigenic peptide and the alpha (2) macroglobulin receptor activity measured is the ability to stimulate a cytotoxic T cell response against the antigenic peptide.

17. A method for identifying a compound that modulates the binding of a heat shock protein to the .alpha.2M receptor, comprising: (a) contacting a heat shock protein with an alpha (2) macroglobulin receptor, or fragment, or analog, derivative or mimetic thereof, in the presence of a test compound; and (b) measuring the amount of heat shock protein bound to the alpha (2) macroglobulin receptor, or fragment, analog, derivative or mimetic thereof, such that if the amount of bound heat shock protein measured in (b) differs from the amount of bound heat shock protein measured in the absence of the test compound, then a compound that modulates the binding of an HSP to the .alpha.2M receptor is identified.

18. The method of claim 65 wherein the solid surface is a microtiter dish.

19. The method of claim 17 wherein the amount of bound heat shock protein is measured by contacting the cell with a heat shock protein-specific antibody.

20. The method of claim 17 wherein the heat shock protein is labeled and the amount of bound heat shock protein is measured by detecting the label.

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21. The method of claim 20 wherein the heat shock protein is labeled with a fluorescent label.

22. A method for identifying a compound that modulates heat shock protein-mediated antigen presentation by alpha (2) macroglobulin receptor-expressing cells comprising: (a) adding a test compound to a mixture of alpha (2) macroglobulin receptor-expressing cells and a complex consisting essentially of a heat shock protein noncovalently associated with an antigenic molecule, under conditions conducive to alpha (2) macroglobulin receptor-mediated endocytosis; (b) measuring the level of stimulation of antigen-specific cytotoxic T cells by the alpha (2) macroglobulin receptor-expressing cells, such that if the level measured in (b) differs from the level of said stimulation in the absence of the test compound, then a compound that modulates heat shock protein-mediated antigen presentation by alpha (2) macroglobulin receptor-expressing cells is identified.

23. A method for detecting a heat shock protein-alpha (2) macroglobulin receptor-related disorder in a mammal comprising measuring the level of activity from an HSP-alpha (2) macroglobulin receptor-mediated process in a patient sample, such that if the measured level differs from the level found in clinically normal individuals, then a heat shock protein-alpha (2) macroglobulin receptor-related disorder is detected.

24. The method of claim 23 comprising contacting a sample derived from a patient with an antibody specific for the alpha (2) macroglobulin receptor under conditions such that immunospecific binding by the antibody.

25. The method of claim 23 comprising contacting a sample derived from a patient with an antibody specific for a heat shock protein under conditions such that immunospecific binding by the antibody.

26. The method of claim 23 comprising contacting a sample derived from a patient with an antibody specific for an HSP-.alpha.2M complex under conditions such that immunospecific binding by the antibody.

27. A method for modulating an immune response comprising administering to a mammal a purified compound that modulates the interaction of a heat shock protein with the alpha (2) macroglobulin receptor.

28. The method of claim 27, in which the compound is an agonist which enhances the interaction of the heat shock protein and the alpha (2) macroglobulin receptor.

29. A method for treating an autoimmune disorder comprising administering to a mammal in need of such treatment a purified compound that interferes with the interaction of a heat shock protein with the alpha (2) macroglobulin receptor.

30. The method of claim 29 in which the compound is an antagonist that interferes with the interaction between the heat shock protein and the .alpha.2M receptor.

31. The method of claim 30, in which the antagonist is an antibody specific for alpha (2) macroglobulin receptor.

32. The method of claim 30, in which the antagonist is an antibody specific for a heat shock protein.

33. The method of claim 30, in which the antagonist is a small molecule.

34. The method of claim 30, in which the antagonist is a peptide.

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35. The method of claim 30, in which the peptide comprises at least 5 consecutive amino acids of alpha (2) macroglobulin receptor (SEQ ID NO.: 1).

36. The method of claim 30, in which the peptide comprises at least 5 consecutive amino acids of alpha (2) macroglobulin (SEQ ID NO.: 3).

37. The method of claim 30, in which the peptide comprises at least 5 consecutive amino acids of a heat shock protein sequence.

38. A method for treating an autoimmune disorder comprising administering to a mammal in need of such treatment a recombinant cell that expresses an alpha (2) macroglobulin receptor which decreases the uptake of a heat shock protein by a functional alpha (2) macroglobulin receptor.

39. A method for increasing the immunopotency of a cancer cell or an infected cell comprising transforming said cell with a nucleic acid comprising a nucleotide sequence that (i) is operably linked to a promoter, and (ii) encodes an alpha (2) macroglobulin receptor polypeptide.

40. A method for increasing the immunopotency of a cancer cell or an infected cell comprising: (a) transforming said cell with a nucleic acid comprising a nucleotide sequence that (i) is operably linked to a promoter, and (ii) encodes an alpha (2) macroglobulin receptor polypeptide, and (b) administering said cell to an individual in need of treatment, so as to obtain an elevated immune response.

41. A recombinant cancer cell transformed with a nucleic acid comprising a riucleotide sequence that (i) is operably linked to a promoter, and (ii) encodes an alpha (2) macroglobulin receptor polypeptide.

42. A recombinant infected cell transformed with a nucleic acid comprising a nucleotide sequence that (i) is operably linked to a promoter, and (ii) encodes an alpha (2) macroglobulin receptor polypeptide.

43. The recombinant cell of claim 41 or 42 which is a human cell.

44. A kit, comprising in one or more containers: (a) an anti-.alpha.2M receptor antibody or a nucleic acid probe capable of hybridizing to an .alpha.2M receptor nucleic acid, (b) a purified heat shock protein, nucleic acid encoding a heat shock protein, or cell expressing a heat shock protein; and (c) instructions for use in detecting a heat shock protein-alpha (2) macroglobulin receptor-related disorder.

45. The kit of claim 44 wherein the antibody or nucleic acid probe is labeled with a detectable marker.

46. The kit of claim 44 further comprising a labeled macroglobulin receptor polypeptide.

47. A kit, in one or more containers, comprising: (a) a purified heat shock protein, nucleic acid encoding a heat shock protein, or cell expressing a heat shock protein; and (b) an alpha (2) macroglobulin receptor polypeptide, nucleic acid encoding an alpha (2) macroglobulin receptor polypeptide, or cell expressing an alpha (2) macroglobulin receptor polypeptide.

48. The kit of claim 47 in which the alpha (2) macroglobulin receptor polypeptide, nucleic acid encoding an alpha (2) macroglobulin receptor polypeptide, or cell expressing an alpha (2) macroglobulin receptor polypeptide is purified.

49. The kit of claim 47 further comprising instructions for use in treating an autoimmune disorder, an infectious disease, or a proliferative disorder.

50. A method for identifying an .alpha.2M receptor fragment capable of binding a heat shock protein, said method comprising: (a) contacting a heat shock protein, or peptide-binding fragment thereof, with one or more alpha (2) macroglobulin receptor fragments; and (b) identifying an .alpha.2M receptor fragment which specifically binds to the heat shock protein, or peptide-binding fragment thereof.

51. A method for identifying an .alpha.2M receptor fragment capable of inducing an HSP-.alpha.2M receptor-mediated process, said method comprising: (a) contacting a heat shock protein with a cell expressing .alpha.2M receptor fragment; and (b) measuring the level of alpha (2) macroglobulin receptor activity in the cell, such that if the level of the HSP-.alpha.2M receptor-mediated process or activity measured in (b) is greater than the level of alpha (2) macroglobulin receptor activity in the absence of the .alpha.2M receptor fragment, then an .alpha.2M receptor fragment capable of inducing an HSP-.alpha.2M receptor-mediated process is identified.

52. The method of claim 51 wherein the alpha (2) macroglobulin receptor activity measured is the ability to interact with the heat shock protein.

53. The method of claim 51 wherein the heat shock protein is non-covalently associated with an antigenic peptide and the alpha (2) macroglobulin receptor activity measured is the ability to re-present the antigenic peptide.

54. The method of claim 51 wherein the heat shock protein is non-covalently associated with an antigenic peptide and the alpha (2) macroglobulin receptor activity measured is the ability to stimulate a cytotoxic T cell response against the antigenic peptide.

55. A method for identifying a heat shock protein fragment capable of binding an .alpha.2M receptor, said method comprising: (a) contacting an .alpha.2M receptor with one or more heat shock protein fragments; and (b) identifying a heat shock protein fragment which specifically binds to the .alpha.2M receptor.

56. A method for identifying a heat shock protein fragment capable of inducing an HSP-.alpha.2M receptor-mediated process, said method comprising: (a) contacting an .alpha.2M receptor fragment with a cell expressing a heat shock protein; and (b) measuring the level of alpha (2) macroglobulin receptor activity in the cell, such that if the level of the HSP-.alpha.2M receptor-mediated process or activity measured in (b) is greater than the level of alpha (2) macroglobulin receptor activity in the absence of said heat shock protein fragment, then a heat shock protein fragment capable of inducing an HSP-.alpha.2M receptor-mediated process is identified.

57. The method of claim 56 wherein the alpha (2) macroglobulin receptor activity measured is the ability to interact with the heat shock protein fragment.

58. The method of claim 56 wherein the heat shock protein fragment is non-covalently associated with an antigenic peptide and the alpha (2) macroglobulin receptor activity measured is the ability to re-present the antigenic peptide.

59. The method of claim 56 wherein the heat shock protein fragment is non-covalently associated with an antigenic peptide and the alpha (2) macroglobulin receptor activity measured is the ability to stimulate a cytotoxic T cell response against the antigenic peptide.

60. A method for identifying a molecule that binds specifically to an .alpha.2M receptor, said method comprising: (a) contacting an .alpha.2M receptor with one or more test molecules under conditions conducive to binding; and (b) identifying one or more test molecules that specifically bind to the .alpha.2M receptor.

61. The method of claim 60 wherein said test molecules are potential immunotherapeutic drugs.

62. A method for screening for molecules that specifically bind to an .alpha.2M receptor comprising: (a) contacting an .alpha.2M receptor with one or more test molecules under conditions conducive to binding; and (b) determining whether any of said test molecules specifically bind to the .alpha.2M receptor.

63. A method for identifying a compound that modulates the binding of an .alpha.2M receptor ligand to the .alpha.2M receptor comprising: (a) contacting an .alpha.2M receptor with an .alpha.2M receptor ligand, or an .alpha.2M receptor-binding fragment, analog, derivative or mimetic thereof, in the presence of one or more test compounds; and (b) measuring the amount of .alpha.2M receptor ligand, or fragment, analog, derivative or mimetic thereof, bound to the .alpha.2M receptor, such that if the amount of bound .alpha.2M receptor ligand measured in (b) differs from the amount of bound .alpha.2M receptor measured in the absence of the test compound, then a compound that modulates the binding of an .alpha.2M receptor ligand to the .alpha.2M receptor is identified.

64. The method of claim 17 or 63, in which the alpha (2) macroglobulin receptor contacted in step (a) is on a cell surface.

65. The method of claim 17 or 63, wherein the alpha (2) macroglobulin receptor is immobilized to a solid surface.

66. The method of claim 1, 64, or 22 in which the heat shock protein is gp96.

67. The method of claim 1, 64, or 22 in which the heat shock protein is hsp90.

68. The method of claim 1, 64, or 22 in which the heat shock protein is hsp70.

69. The method of claim 1, 64, or 22 in which the heat shock protein is calreticulin.

70. A method for identifying a compound that modulates the interaction between the .alpha.2M receptor and an .alpha.2M receptor ligand, comprising: (a) contacting an .alpha.2M receptor with one or more test compounds; and (b) measuring the level of .alpha.2M receptor activity or expression, such that if the level of activity or expression measured in (b) differs from the level of .alpha.2M receptor activity in the absence of one or more test compounds, then a compound that modulates the interaction between the .alpha.2M receptor and an .alpha.2M receptor ligand is identified.

71. The method of claim 63 or 70 wherein the .alpha.2M receptor ligand is .alpha.2 macroglobulin.

72. A method for identifying a compound that modulates antigen presentation by .alpha.2M receptor-expressing cells comprising: (a) adding one or more test compounds to a mixture of .alpha.2M receptor-expressing cells and a complex comprising an .alpha.2M receptor ligand and an antigenic molecule, under conditions conducive to .alpha.2M receptor-mediated endocytosis; (b) measuring the level of stimulation of antigen-specific cytotoxic T cells by the .alpha.2M receptor-

expressing cells, such that if the level measured in (b) differs from the level of said stimulation in the absence of the one or more test compounds, then a compound that modulates antigen presentation by .alpha.2M receptor-expressing cells is identified.

73. The method of claim 22 or 72, in which the measuring stimulation of antigen-specific cytotoxic T cells by the .alpha.2M receptor-expressing cells of step (b) comprises: (i) adding the alpha (2) macroglobulin receptor-expressing cells formed in step (a) to T cells under conditions conducive to the activation of the T cells; and (ii) comparing the level of activation of said cytotoxic T cells with the level of activation of T cells by an alpha (2) macroglobulin receptor-expressing cell formed in the absence of the test compound, wherein an increase of decrease in level of T cell activation indicates that a compound that modulates heat shock protein-mediated antigen presentation by alpha (2) macroglobulin receptor-expressing cells is identified.

74. A method for modulating an immune response comprising administering to a mammal a purified compound that binds to the .alpha.2M receptor, in an amount effective to modulate an immune response in the mammal.

75. A method for treating or preventing a disease or disorder comprising administering to a mammal a purified compound that binds to the .alpha.2M receptor, in an amount effective to treat or prevent the disease or disorder in the mammal.

76. The method of claim 75 wherein the disease or disorder is cancer or an infectious disease.

77. A method for treating an autoimmune disorder comprising administering to a mammal in need of such treatment a purified compound that binds to the .alpha.2M receptor, in an amount effective to treat an autoimmune disorder in the mammal.

78. A method for stimulating an immune response in a patient comprising administering to said patient blood which has been withdrawn from said patient and treated to remove an .alpha.2M receptor ligand.

79. The method of claim 78 further comprising administering to said patient a heat shock protein or a heat shock protein-antigenic peptide complex.

80. A method for stimulating an immune response in a patient comprising: (a) removing a .alpha.2M receptor ligand from blood withdrawn from said patient; and (b) returning at least a portion of the .alpha.2M receptor ligand-depleted blood to said patient.

81. A method for stimulating an immune response in a patient comprising: (a) withdrawing blood from said patient; (b) removing a .alpha.2M receptor ligand from said blood; and (c) returning at least a portion of the .alpha.2M receptor ligand-depleted blood to said patient.

82. The method of claim 81 further comprising after step (a) and before step (c) the step of adding a heat shock protein or a heat shock protein-antigenic peptide complex to said blood.

83. The method of claims 80 or 81 wherein removing a .alpha.2M receptor ligand from the blood comprises the step of contacting the blood with a solid phase attached to a .alpha.2M receptor ligand-binding molecule for a time period and under conditions sufficient to allow binding of .alpha.2M receptor ligand to the .alpha.2M receptor ligand-binding molecule solid phase.

84. The method of claim 83 wherein the .alpha.2M receptor ligand-binding molecule .alpha.2M receptor, or a fragment thereof.

85. The method of claim 83 wherein said .alpha.2M receptor ligand-binding molecule does not bind a heat shock protein.

86. The method of claim 85 wherein the .alpha.2M receptor ligand-binding molecule is an .alpha.2M receptor ligand-specific antibody, or a fragment thereof.

87. The method of claims 80 or 81 wherein an apheresis system is used in said removing step.

88. The method of claim 81 wherein blood is withdrawn manually in said withdrawing step.

89. The method of claim 80 or 81 wherein said removing step comprises separating the plasma from said blood and treating said plasma to remove said .alpha.2M receptor ligand.

90. The method of claim 78 wherein said blood is administered to said patient by syringe.

91. The method of claim 78 wherein said blood is administered to said patient by an intravenous drip.

92. The method of claim 80 or 81 wherein said blood is returned to said patient by syringe.

93. The method of claim 80 or 81 wherein said blood is returned to said patient by an intravenous drip.

94. A kit comprising in one or more containers a solid phase chromatography column with a purified .alpha.2M receptor ligand binding molecule attached thereto, such that withdrawn blood can be run over the column to deplete the blood of a .alpha.2M receptor ligand.

95. The kit of claim 94 wherein the .alpha.2M receptor ligand binding molecule does not bind heat shock proteins.

96. The method of claim 78, 80, or 81 wherein the .alpha.2M receptor ligand is .alpha.2M, a lipoprotein complex, lactoferrin, tissue-type plasminogen activator, urokinase-type plasminogen activator, or an exotoxin.

Previous Doc Next Doc Go to Doc#